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<p>(21) International Application Number: PCT/GB91/00119</p> <p>(22) International Filing Date: 28 January 1991 (28.01.91)</p> <p>(30) Priority data: 9001878.9 26 January 1990 (26.01.90) GB</p> <p>(71) Applicant (for all designated States except US): BEAM TECH LIMITED [GB/GB]; Tarvin Mill Industrial Estate, Tarvin, Chester CH3 8JF (GB).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): GILDING, Dennis, Keith [GB/GB]; Nepenthe, Wettenhall, Cheshire CW7 4DL (GB).</p> <p>(74) Agent: ATKINSON, Peter, Birch; Marks & Clerk, Suite 301, Sunlight House, Quay Street, Manchester M3 3JY (GB).</p>	<p>(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: ALGINATE MATERIALS</p> <p>(57) Abstract</p> <p>An alginate material useful particularly as a wound dressing incorporates cations selected from zinc, copper, silver, cerium, manganese, cobalt, or any cation which is an enzyme cofactor, save that the cation is not solely calcium, sodium or a mixture of these two cations.</p>		

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ALGINATE MATERIALS

The present invention relates alginate materials which are useful particularly (but not exclusively) for wound dressings.

It is known that alginate materials have haemostatic and wound healing properties and may be used in various types of wound dressing (see for example EP-A- 0 236 104 (Courtaulds)).

Conventionally, alginates for wound dressings are prepared by spinning a solution of sodium alginate into a bath containing calcium ions (usually provided by calcium chloride) so that alginate material precipitates in the form of the insoluble calcium salt. For certain applications, it may be desirable for the alginate to have a greater degree of solubility in body fluids, in which case the calcium alginate may be treated in a bath of sodium ions so that some of the calcium is replaced by sodium to provide a more soluble form.

The alginates are highly hydrophilic and have thus found particular use in the dressing of "highly exuding" wounds where this absorbing allows comparatively large quantities of exudate to be absorbed before the alginate material dissolves.

It is a object of the present invention to provide alginate materials with improved properties for the treatment of wounds.

According to the present invention there is provide an alginate material which comprises of zinc, copper, silver, cerium, manganese, or cobalt cations and/or any cation which is an enzyme co-factor, save that the cation is not solely calcium, sodium or a mixture of these two cations. Enzyme co-factors include Mg^{2+} , Co^{2+} , Mn^{2+} and Fe^{3+} ions.

In the alginate material of the invention, the cation (or mixture of abovementioned cations) provide exchangeable

ions which have useful wound healing properties and the alginate serves as a base material for the delivery of these cations to the wound site. The absorbency of the alginate material is an added advantage.

Assuming that the cation has an oxidation state of $n+$ the minimum amount of the cation incorporated in the alginate material is preferably $(1/2n)$ moles (of cation) per mole of sugar residue in the alginate. Thus, for a divalent ion ($n=2$) the minimum amount is preferably 0.25 moles. Similarly for a monovalent ion ($n=1$) the preferred minimum amount is 0.5 moles (of cation). The preferred maximum amount for the cation is $(1/n)$ moles per mole of sugar residue in the alginate. Thus the preferred maximum for divalent cation ($n=2$) is 0.5 moles.

The ions shown below have the indicated properties:

<u>Ion</u>	<u>Wound Healing Property</u>
Zn^{2+}	promotes healing
Ag^+	bactericidal action
Cu^{2+}	anti-microbial, wound flushing
Ce^{2+}	anti-immunosuppressant
Mn^{2+}	enzyme (oxidase) co-factor
Co^{2+}	enzyme co-factor

It will thus be appreciated that alginate materials of the invention may be used in a wide range of wound healing applications. One particular application is for the treatment of leg ulcers which might contain in excess of 10^5 organisms/ml. In this case, an alginate material containing copper ions may initially be applied to the ulcer and would cause the wound to flush itself. Subsequently, a further alginate material containing zinc ions may be applied to the ulcer to promote wound healing.

In order to assist delivery of the cations into the wound, it is possible to use an iontophoretic technique so as to "drive" the ions into the wound.

The alginate material may be in the form of a porous

membrane but is more preferably in the form of a porous fibrous material or of a particulate material of sufficiently small size for formulation into an aerosol (which may then be sprayed onto a wound). The use of a porous fibrous material (produced, for example, as described below) is particularly advantageous because of the high internal surface area avoidable for ion-exchange.

Such a fibrous material may be produced by spinning a solution of a soluble alginate (particularly sodium or magnesium alginate) into a bath containing the cations to be incorporated in the final alginate material. The solution may, for example, be spun into a bath by dissolving the chloride or nitrate of zinc and/or silver in water.

Such fibrous materials may be supported in any suitable way for application to a wound site. The support may, for example, comprise a porous textile dressing or a porous membrane or a porous polymeric membrane comprised of a hydrophobic polymer defining a porous (particularly microporous) structure and a hydrophilic polymer provided at the surfaces, including the internal pore surfaces, of the hydrophobic polymer. Such a membrane is disclosed in WO-A-90/11820 (Beam Tech).

Particulate alginate material (for formulation into an aerosol) may be produced by subjecting particulate calcium alginate material to an ion exchange process with the appropriate cation(s).

An alginate membrane may be produced by preparing an aqueous solution of a soluble alginate material, forming the solution into the shape of a membrane, and treating the thus formed membrane precursor with a liquid containing cations which precipitate alginate material from solution as a porous membrane.

The precipitation bath may be aqueous or may be or include a water miscible organic solvent (e.g. DMSO, DMF).

CLAIMS

1. An alginate material which incorporates cations selected from zinc, copper, silver, cerium, manganese, cobalt, or any cation which is an enzyme cofactor, save that the cation is not solely calcium, sodium or a mixture of these two cations.
2. A material as claimed in claim 1 including an enzyme cofactor selected from Mg^{2+} , Co^{2+} , Mn^{2+} , and Fe^{3+} .
3. An alginate material as claimed in claim 1 or 2 wherein the alginate material is in the form of a fibre, a membrane, a film, or in the form of particles.
4. An alginate material as claimed in claim 3 wherein the alginate material comprises particles in the form of an aerosol.
5. A wound dressing comprising an alginate material as claimed in any one of claims 1 to 3.
6. A wound dressing as claimed in claim 4 wherein the alginate material is associated with a porous membrane comprised of a hydrophobic polymer defining the porous structure and a hydrophilic polymer provided at the surfaces, including the internal pore surfaces, of the hydrophobic polymer.
7. A method of producing an alginate material as claimed in claim 1 comprising providing a solution of a soluble alginate (preferably sodium or magnesium alginate) in a precipitation bath which contains at least one of said cations.
8. A method as claimed in claim 6 wherein said soluble alginate is spun into the bath to produce a fibre.
9. A method as claimed in claim 6 wherein said solution of the soluble alginate material is formed into the shape of a membrane and introduced into the precipitation bath.
10. A material as claimed in any one of claims 1 to 4 wherein the cation has an oxidation state of $n+$ and the amount of the cation present in the alginate material is at least $(1/2n)$ moles per mole of sugar residu .

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 91/00119

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶				
According to International Patent Classification (IPC) or to both National Classification and IPC: Int.Cl. 5 A61L15/28				
II. FIELDS SEARCHED				
Minimum Documentation Searched ⁷				
Classification System	Classification Symbols			
Int.Cl. 5	A61L			
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸				
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹				
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³		
X	GB,A,1328088 (WALLACE, CAMERON AND COMPANY LIMITED) 30 August 1973 see page 1, lines 38 - 53 see page 3, lines 5 - 24 see claims 1-11	1-5, 7		
X	EP,A,243069 (JOHNSON & JOHNSON PRODUCTS INC.) 28 October 1987 see page 2, lines 25 - 29; claims 1-14	1-3, 5		
A	GB,A,976301 (CALMIC LIMITED) 25 November 1964 see claims 1-11	1		
A	GB,A,629419 (JOHNSON & JOHNSON LIMITED) 20 August 1949 see claims 1-14	1		

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¹⁰ Special categories of cited documents: <table border="0" style="width: 100%;"> <tr> <td style="vertical-align: top; width: 50%;"> ^{"A"} document defining the general state of the art which is not considered to be of particular relevance ^{"E"} earlier document but published on or after the international filing date ^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) ^{"O"} document referring to an oral disclosure, use, exhibition or other means ^{"P"} document published prior to the international filing date but later than the priority date claimed </td> <td style="vertical-align: top; width: 50%;"> ^{"I"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention ^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step ^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. ^{"A"} document member of the same patent family </td> </tr> </table>			^{"A"} document defining the general state of the art which is not considered to be of particular relevance ^{"E"} earlier document but published on or after the international filing date ^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) ^{"O"} document referring to an oral disclosure, use, exhibition or other means ^{"P"} document published prior to the international filing date but later than the priority date claimed	^{"I"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention ^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step ^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. ^{"A"} document member of the same patent family
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IV. CERTIFICATION				
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report			
24 APRIL 1991	30.05.91			
International Searching Authority	Signature of Authorized Officer			
EUROPEAN PATENT OFFICE	ESPINOSA Y CARR			

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	GB,A,1255155 (WALLACE, CAMERON & COMPANY LIMITED) 01 December 1971 see claims 1-18 ---	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

PCT/GB 91/0011
SA 43985

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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24/04/91

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-1328088	30-08-73	None	
EP-A-243069	28-10-87	AU-B- 601726 AU-A- 7183187	20-09-90 22-10-87
GB-A-976301		None	
GB-A-629419		None	
GB-A-1255155	01-12-71	None	

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82